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(56) Documents Cited
**EP 0377518 A2 EP 0271193 A2 EP 0108218 A2
WO 92/02209 A1 WO 92/01446 A1 US 3634584 A
Curr.Ther.Res.47 pages 869-878 (1990) British National
Formulary No.25 (March 1993) page 181-see MST
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(54) **Sustained release morphine compositions**

(57) An orally administered sustained release dosage unit form containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient, which composition gives a peak plasma level at from 1.0 to 3.5 hours after administration. The morphine dosage form is suitable for once-a-day administration. It is preferably in the form of a capsule filled with pellets comprising morphine and a hydrophobic release control material such as a natural or synthetic wax or oil e.g. hydrogenated vegetable or castor oil.

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SUSTAINED RELEASE COMPOSITIONS

This invention is concerned with improvements in and relating to sustained release compositions and, more particularly, is concerned with sustained release orally administerable dosage unit forms containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient.

Morphine is an opioid analgesic well established for use in the treatment of pain, especially moderate to severe pain. Morphine-containing compositions in sustained release form are currently commercially available as so-called "twice-a-day" formulations, that is formulations having a duration of activity of 12 hours or more and accordingly requiring to be administered twice a day.

It is an object of the present invention to provide a morphine-containing sustained release orally administrable dosage unit form which has an effective duration of activity of 24 hours or more and, hence, is suitable for administration on a once daily basis.

It has surprisingly been found, in accordance with the present invention, that effective therapeutic

activity over a period of 24 hours or more may be obtained from a morphine-containing sustained release formulation which gives an in vivo peak plasma level relatively early after administration, that is from 1.0 to 3.5 hours after administration.

Accordingly, one embodiment of the invention provides an orally administrable sustained release dosage unit form containing morphine, or a pharmaceutically acceptable salt thereof, as active ingredient which formulation gives a peak plasma level at from 1.0 to 3.5 hours, preferably 2 to 3 hours, after administration.

When the morphine is administered as morphine sulphate and the method of plasma analysis is high performance liquid chromatography, the peak plasma level of morphine (per ml of plasma) is preferably from 0.5×10^{-7} to 7.5×10^{-7} times the amount of morphine sulphate orally administered. When morphine base or a salt other than the sulphate is administered, the preferred ratio of drug administered to peak plasma level should be adjusted according to the molecular weight of the base or salt.

The dosage unit form in accordance with the invention should contain sufficient morphine, or salt thereof, to give therapeutic activity over a period of at least 24 hours. The actual amount of morphine, or salt, in any particular dosage form will of course depend upon a number of variables including (i) the number of dosage unit forms intended to be administered at any one time and (ii) the intended dosage for any particular patient. Conveniently, however, dosage unit forms in accordance with the invention will contain from 10 to 500 mg of morphine (calculated as morphine sulphate) and thus, for example, typical dosage unit forms in accordance with the invention are those containing 20, 30, 60, 90, 120, 150 and 200 mg of morphine (calculated as above).

It has further been found, in accordance with the present invention, that in order to achieve the desired time of peak plasma level and to provide effective activity over a period of at least 24 hours, the in vitro release characteristics of the formulation (when measured by the modified Ph.Eur. Basket method at 100 rpm in 900 ml aqueous buffer (pH 6.5) at 37°C) are as set out below:

hours after start of test	% morphine (salt) suitable	released preferred
2	15-50	25-50
4	20-65	30-65
6	25-75	40-75
12	40-90	60-90
18	55-100	70-100
24	65-100	80-100

The compositions of the invention may be provided in a variety of forms, for example as tablets or capsules containing granules, spheroids or pellets. Commonly, the composition will comprise the active ingredient (morphine or salt thereof) together with a diluent which may serve to delay release of the active ingredient or which may be coated with a coating which serves to control the rate of release of the active ingredient. A preferred form of dosage unit form in accordance with the invention comprises a capsule filled with pellets essentially comprising the active ingredient and a hydrophobic release control material. In particular, the pellets are preferably prepared by a so-called "melt pelletisation" process. In essence, such process comprises forming a mixture of dry particulate active

ingredient and fusible release control material and pelletising the mixture in a high speed mixer at a rate and energy input such that sufficient energy is supplied to the fusible material or melt or soften it whereby it forms pellets with the particulate active ingredient. The resultant pellets, after cooling, are suitably sieved to give pellets having a particle size range from 0.1 to 3.0 mm, preferably 0.25 to 2.0 mm.

When using such a melt pelletisation technique it has been found that, in order to most readily achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be pelleted should comprise two essential ingredients namely:

- (a) active ingredient (morphine or salt thereof); and
- (b) hydrophobic fusible carrier or diluent; optionally together with
- (c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil or hydrogenated castor oil, and suitably has a melting point of from 35 to 100°C, preferably 45 to 90°C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Only a relatively small amount of component (c) is required to modify the release characteristics of the formulation and thus, for example, this component suitably forms from 0.01 to 20% by weight, more preferably 0.01 to 15% by weight of the total weight of the pellets. We have found that the total amount of active ingredient in the composition may vary within wide limits, for example from 10 to 60% by weight thereof.

Alternatively the morphine (or salt thereof) may be formulated (e.g. by dry or wet granulation or by blending) in a controlled release mixture formed of components other than fusible components. Suitable materials for inclusion in a controlled release matrix include, for example

- (a) Hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, protein derived materials, nylon, acrylic resins, polylactic acid, polyvinylchloride, starches, polyvinylpyrrolidones, cellulose acetate phthalate. Of these polymers,

cellulose ethers especially substituted cellulose ethers such as alkylcelluloses (such as ethylcellulose), C_1 - C_6 hydroxyalkylcelluloses (such as hydroxypropylcellulose and especially hydroxyethyl cellulose) and acrylic resins (for example methacrylates such as methacrylic acid copolymers) are preferred. The controlled release matrix may conveniently contain between 1% and 80% (by weight) of hydrophilic or hydrophobic polymer.

- (b) Digestible, long chain (C_8 - C_{50} , especially C_8 - C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, hydrogenated vegetable oils such as Cutina (Trade Mark), fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), glyceryl esters of fatty acids for example glyceryl monostearate mineral oils and waxes (such as beeswax, glycowax, castor wax or carnauba wax). Hydrocarbons having a melting point of between 25°C and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The matrix may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.
- (c) Polyalkylene glycols. The matrix may contain up to 60% (by weight) of at least one polyalkylene glycol.

A suitable matrix comprises one or more cellulose ethers or acrylic resins, one or more C_{12} - C_{36} , preferably C_{14} - C_{22} , aliphatic alcohols and/or one or more hydrogenated vegetable oils.

A particularly suitable matrix comprises one or more alkylcelluloses, one or more C_{12} - C_{36} , (preferably C_{14} - C_{22}) aliphatic alcohols and optionally one or more polyalkylene glycols.

Preferably the matrix contains between 0.5% and 60%, especially between 1% and 50% (by weight) of the cellulose ether.

The acrylic resin is preferably a methacrylate such as methacrylic acid copolymer USNF Type A (Eudragit L, Trade Mark), Type B (Eudragit S, Trade Mark), Type C (Eudragit L 100-55, Trade Mark), Eudragit NE 30D, Eudragit E, Eudragit RL and Eudragit RS. Preferably the matrix contains between 0.5% and 60% by weight, preferably between 1% and 50% by weight of the acrylic resin.

In the absence of polyalkylene glycol, the matrix preferably contains between 1% and 40%, especially between 2% and 36% (by weight) of the aliphatic alcohol. When polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol

and the polyalkylene glycol preferably constitutes between 2% and 40%, especially between 2 and 36% (by weight) of the matrix.

The polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 200 and 15000 especially between 400 and 12000.

The morphine-containing controlled release matrix can readily be prepared by dispersing the active ingredient in the controlled release system using conventional pharmaceutical techniques such as melt granulation, wet granulation, dry blending, dry granulation or coprecipitation.

Another form of sustained release formulation comprises spheroids obtained by spheronizing the morphine (or salt thereof) with a spheronizing agent such as microcrystalline cellulose.

In order that the invention may be well understood the following examples are given by way of illustration only.

EXAMPLES

Pellets, having the formulations given in Table I below, were prepared by the steps of:-

- (i) placing the ingredients, in a total amount by weight of 10 kg, in the bowl of a 70 litre capacity. Collette Gral mixer (or equivalent), equipped with variable speed mixing and granulating blades;
- (ii) mixing the ingredients while applying heat until the contents of the bowl are pelletised;
- (iii) discharging the pellets from the mixer and sieving them to separate out the pellets collected between 0.5 and 2 mm aperture sieves.

Table I

Example No.	1	2	3	4	5	6	7	8
Morphine Sulphate (wt.%)	15	15	15	23	55	55	55	55
Hydrogenated castor oil U.S.N.F. (wt.%)	77	76	75	70	-	-	-	-
Hydrogenated vegetable oil U.S.N.F. (wt.%)	-	-	-	-	42.8	45	44.95	42.0
Polyethylene glycol 6000 U.S.N.F. (wt.%)	8	9	10	7	0.2	-	0.05	-
Dicalcium phosphate anhydrous USP (wt.%)	-	-	-	-	2	-	-	3

The in vitro release rates of the products of Examples 1, 2, 3 and 5 were assessed by the modified Ph.Eur. Basket method as noted above. For each of the products, six samples of the pellets, each sample containing a total of 30 mg of morphine sulphate, were tested. The results set out in Table II below give the mean values for each of the six samples tested.

TABLE II

Hours after start of test	<u>Product of Example</u>			
	1 (% morphine released)	2	3	5
2	19	25	33	44
4	27	36	49	57
6	34	45	62	66
8	41	52	72	72
12	53	64	86	81
18	66	77	96	89
24	76	86	101	92

Pharmacokinetic studies in healthy human volunteers have indicated peak plasma levels of from 2.5 to 21.6 ng/ml of morphine at times between 1.0 and 3.5 hours following administration of a single capsule containing pellets of Examples 1, 2, 3 or 5 in an amount sufficient to provide a morphine sulphate dose of 30 mg.

CLAIMS:

1. An orally administrable sustained release dosage unit form containing morphine, or a pharmaceutically salt thereof, as active ingredient, which composition gives a peak plasma level at 1.0 to 3.5 hours after administration.
2. A pharmaceutical composition as claimed in claim 1 containing from 10 to 500 mg of morphine (calculated as morphine sulphate).
3. A pharmaceutical composition as claimed in claim 1 or claim 2 having in vitro release characteristics such that the formulation (when assessed by the modified Ph.Eur. Basket Method at 100 rpm in 900 ml aqueous buffer, pH 6.5, at 37°C), releases from 15 to 50% of active ingredient two hours after start of test, 20 to 65% at 4 hours after start of test; 25% to 75% at 6 hours after start of test; 40 to 90% at 12 hours after start of test, from 55 to 100% at 18 hours after start test and 65 to 100% at 24 hours after start of test.
4. A pharmaceutical composition as claimed in any one of the preceding claims comprising a capsule filled with pellets essentially comprising the active ingredient and a hydrophobic release control material.

5. A pharmaceutical composition as claimed in claim 4 which has been prepared by a melt pelletisation process.

6. A pharmaceutical composition as claimed in claim 4 or claim 5 also containing from 00.1 to 20% by weight, based on the total weight of the pellets, of a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

7. A pharmaceutical composition as claimed in claim 1 substantially as hereinbefore described with reference to the Examples.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report)	Application number GB 9315467.2
Relevant Technical Fields (i) UK Cl (Ed.L) A5B (BLM) (ii) Int Cl (Ed.5) A61K 9/16, 9/52 Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES : DIALINDEX (MEDICINE), WPI, CAS-ONLINE	Search Examiner J F JENKINS
	Date of completion of Search 16 NOVEMBER 1993
	Documents considered relevant following a search in respect of Claims :- 1 TO 7

Categories of documents

X: Document indicating lack of novelty or of inventive step.	P: Document published on or after the declared priority date but before the filing date of the present application.
Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.	E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.
A: Document indicating technological background and/or state of the art.	&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
X	EP 0377518 A2 (F H FAULDIN G & CO) - see page 9 lines 8 to 27 and Examples	1-4
Y	EP 0271193 A2 (EURCELTIQUE) - whole document	1-4 and 6
Y	EP 0108218 A2 (VEREX LABS) - see page 7 line 27	1-4 and 6
X	WO 92/02209 A1 (ALACHE) - see Examples 1, 2 and 7	1-4
Y	WO 92/01446 A1 (APS RESEARCH) - see pge 2 line 26 - page 3 line 2	1-6
Y	US 3634584 (AMERICAN HOME PRODUCTS) - see column 4 line 58	1-4 and 6
X	Curr Ther Res 47 pages 869-878 (1990) (R F Kaiko et al)	1-4
A	British National Formulary No 25 (March 1993) page 181 - see MST - Continus	1

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